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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
31 January 2013

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(54) Title: CD3-BINDING MOLECULES CAPABLE OF BINDING TO HUMAN AND NON-HUMAN CD3

(57) Abstract: CD3-binding molecules capable of binding to human and non-human CD3, and in particular to such molecules that are cross-reactive with CD3 of a non-human mammal (e.g., a cynomolgus monkey) are presented. Uses of such antibodies and antigen-binding fragments in the treatment of cancer, autoimmune and/or inflammatory diseases and other conditions are presented.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/38219

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/00 (2012.01)
USPC - 530/388.22
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 530/388.22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 530/388.22; 435/69.6, 328 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBASE (EP, WO, US); Google Scholar; GenCore sequence search (AA)
Search terms: CD3, ant-CD3, anti-human CD3, cross-reactive, bivalent, VL domain, VH domain, cancer, autoimmune, inflammatory

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0252683 A1 (KISCHEL et al.) 8 October 2009 (08.10.2009). Especially SEQ ID NO: 194, para [0001], [0016].	1
A	US 2010/0150918 A1 (KUFER et al.) 17 January 2010 (17.01.2010) abstract; para [0082]; [0084]	1

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2012 (12.11.2012)	07 DEC 2012

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.4.1

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-18
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-- Please see extra sheet --

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-3, limited to SEQ ID NOs: 16 and 36 (i.e. claim 1).

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/38219

Continuation of Box III: Lack of Unity of Invention

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+: Claims 1-3, directed to a CD3-binding molecule comprising an antigen-binding fragment of an antibody, wherein said antigen -binding fragment comprises an antibody CD3-specific VL domain and an antibody CD3-specific VH domain, wherein said CD3-specific VL domain and said CD3-specific VH domain form an antigen-binding domain capable of immunospecifically binding to both an epitope of human CD3 and to an epitope of the CD3 of a non-human mammal, wherein:
(1) said CD3-specific VL domain is selected from the group consisting of:
h-mab2 VL-1 (SEQ ID NO: 16); h-mab2 VL-2 (SEQ ID NO:18); h-mab2 VL-3 (SEQ ID NO:20); h-mab2 VL-4 (SEQ ID NO:22); h-mab2 VL-5 (SEQ ID NO: 24); hmab2 VL-6 (SEQ ID NO: 26); h-mab2 VL-7 (SEQ ID NO: 28); h-mab2 VL-8 (SEQ ID NO: 30); h-mab2 VL-9 (SEQ ID NO: 32); and h-mab2 VL-10 (SEQ ID NO: 34);
and said CD3-specific VH domain is selected from the group consisting of:
hmab2 VH-1 (SEQ ID NO:36); h-mab2 VH-2 (SEQ ID NO:38); h-mab2 VH-3 (SEQ ID NO:40); h-mab2 VH-4 (SEQ ID NO:42); h-mab2 VH-5 (SEQ ID NO:44); h-mab2 VH-6 (SEQ ID NO:46); h-mab2 VH-6L (SEQ ID NO:54); h-mab2 VH-7 (SEQ ID NO:48); h-mab2 VH-8 (SEQ ID NO:50); hmab2 VH-8L (SEQ ID NO: 55); h-mab2 VH-8 di-I (SEQ ID NO:56); h-mab2 VH-8 di-2 (SEQ ID NO:57); h-mab2 VH-6M (SEQ ID NO:72); h-mab2 VH-8M (SEQ ID NO:74); h-mab2 VH-2k (SEQ ID NO:87); and h-mab2 VH-5k (SEQ ID NO:88); or
(II) said CD3-specific VL domain is selected from the group consisting of: h-mabl VL-1 (SEQ ID NO:10) and h-mabl VL-2 (SEQ ID NO: 12), and said CD3-specific VH domain is hmab1 VH (SEQ ID NO:14); wherein the first invention is limited to the first specified VL - h-mab2 VL-1 (SEQ ID NO: 16) and the first specified VH - hmab2 VH-1 (SEQ ID NO: 36)(Claim 1) (applicants may opt for additional VL and VH sequence pairs to be searched by specifying the VL and VH sequences, and paying an additional invention search fee for each elected pair of sequences).

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical features of the claims of Groups I+ are the specific VL and VH sequences of the claimed antibodies or antigen binding fragments, wherein each pair of sequences produces a unique antigen binding fragment.

The common technical elements shared by the above groups, that they are related to a CD3-binding molecule comprising an antigen-binding fragment of an antibody, wherein said antigen-binding fragment comprises an antibody CD3-specific VL domain and an antibody CD3-specific VH domain, wherein said CD3-specific VL domain and said CD3-specific VH domain form an antigen-binding domain capable of immunospecifically binding to both an epitope of human CD3 and to an epitope of the CD3 of a non-human mammal, does not represent an improvement over the prior art of US 2009/0252683 A1 to Kischel et al., which teaches "a "bispecific single chain antibody" denotes a single polypeptide chain comprising two binding domains. Each binding domain comprises one variable region from an antibody heavy chain ("VH region"), wherein the VH region of the first binding domain specifically binds to said first molecule, i.e. the CD3 molecule, and the VH region of the second binding domain specifically binds to a cell surface antigen, as defined in more detail below. The two binding domains are optionally linked to one another by a short polypeptide spacer generally comprising on the order of 5 amino acids. Each binding domain may additionally comprise one variable region from an antibody light chain ("VL region"), the VH region and VL region within each of the first and second binding domains being linked to one another via a polypeptide linker, for example of the type disclosed and claimed in EP 623679 B1, but in any case long enough to allow the VH region and VL region of the first binding domain and the VH region and VL region of the second binding domain to pair with one another such that, together, they are able to specifically bind to the respective first and second molecules" (para [0019]), further wherein "the first binding domain of the bispecific single chain antibody as defined herein binds to human CD3 and to non-chimpanzee primate CD3" (para [0021]).

Therefore, the inventions of Groups I+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.